FEB 02 2000

NDA 19-190/S-034
NDA 19-192/S-033

Wyeth-Ayerst Laboratories
Attention: Joseph S. Sonk, Ph.D
Senior Director, Women's Health Care Products, U.S. Regulatory Affairs
P. 0. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

Please refer to your supplemental new drug applications dated March 19, 1998, received March 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Triphasil-28 (levonorgestrel and ethinyl estradiol) Tablets and Triphasil-21 (levonorgestrel and ethinyl estradiol) Tablets.

These supplemental new drug applications provide for revisions to the Clinical Pharmacology section of the Physician Package Inserts in keeping with Agency initiative of standardizing the content and presentation of the Clinical Pharmacology section of the label. The following text additions (highlighted) were proposed by you:

Clinical Pharmacology

> "Combination oral contraceptives primarily act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucous (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). Gonadotropin suppression leads to decreased ovarian production of androgens including testosterone. Additionally, Triphasil increases sex hormone binding globulin (SHBG), resulting in lower serum free testosterone."

PHARMACOKINETICS

Absorption

"Levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%). Levonorgestrel is not subject to first-pass metabolism (or enterohepatic circulation and therefore does not undergo variations in absorption after oral administartion). Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver the bioavailability of ethinyl estradiol is between 38% and 48%."

"There have been no formal multi-dose studies conducted using Triphasil. However, a multi-dose study was done in 22 women using a monophasic, low dose combination of 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol. Maximum serum concentrations of levonorgestrel were found to be 2.8 ± 0 9 ng/ml (mean ± SD) at 1.6 ± 0.9 hours after a single dose, reaching steady state at day 19. Observed levonorgestrel concentrations increased from day 1 to days 6 and 21 by 34 % and 96% respectively. Unbound levonorgestrel concentrations subsequently increased from day 1 to days 6 and 21 by 25% and 83%, respectively, however, the accumulation of unbound levonorgestrel was approximately 14% less than total levonorgestrel accumulation. The kinetics of total levonorgetstrel were non-linear due to an increase in binding of levonorgestrel to SHBG, which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol. Ethinyl estradiol reached maximum serum concentrations of 62 ±21 pg/mL at 1.5 ± 0.5 hours after a single dose, reaching steady state at day 6. Ethinyl estradiol concentrations increased by 19% from days i to 21 consistent with an elimination half-life of 18 hours."

"Single dose studies with Triphasil have been conducted with the following data reported below in table 1. Plasma concentrations have been corrected below to reflect single tablet dosing/day."

TABLE 1: MEAN (SD) PHARMACOKINETIC PARAMETERS OF TRIPHASIL IN SINGLE-DOSE STUDIES

Levonorgestrel

Dose LNG/EE µg	Cmax ng/mL	tmax h	t½ h	AUG ng•h/mL
50/30	1.7 (0.2)	1.2 (0.1)	23 (2.0)	17 (3.0)
75/40	2.1 (0.3)	1.5 (0.2)	15 (1.2)	21 (4.0)
125/30	2.5 (0.4)	1.6 (0.1)	23 (1.4)	35 (6.0)

Ethinyl Estradiol

Dose LNG/EE µg	Cmax pg/mL	tmax h	tmax h	AUC pg•h/mL
50/30	141 (18)	1.4 (0.1)	8.1 (1.0)	1125 (226)
75/40	179 (25)	1.6 (0.2)	14 (1.7)	2177 (488)
125/30	129 (23)	1.6 (0.1)	7.3 (1.0)	2149 (335)

Distribution

"Levonorgestrel is bound to SHBG and albumin. Levonorgestrel has high binding affinity for SHBG that is 60% of that of testosterone. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but will induce SHBG synthesis."

Metabolism

Levonorgestrel: "The most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α,1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α,5β-tetrahydro-levonorgestrel, while excretion occurs predominately in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users."

Ethinyl estradiol: "Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation."

Excretion
"The elimination half-life for levonorgetrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. The elimination half life of ethinyl estradiol is 18 ± 4.7 hours at steady state."

SPECIAL POPULATIONS

Hepatic Insufficiency
"No formal studies have evaluated the effect of hepatic disease on the disposition of Triphasil. However, steroid hormones may be poorly metabolized in patients with impaired liver function."

Renal Insufficiency
"No formal studies have evaluated the effect of renal disease on the disposition of Triphasil"

Drug-Drug Interactions
"Interactions between ethinyl estradiol and other drugs have been reported in the literature."

- **Interactions with Absorption:** "Diarrhea may increase gastrointestinal motility and reduce hormone absorption. Similarly, any drug which reduces gut transit time may reduce hormone concentrations in the blood."

- **Interactions with Metabolism:**
  Gastrointestinal wall: "Sulfation of ethinyl estradiol has been shown to occur in the gastrointestinal (GI) wall. Therefore, drugs which act as competitive inhibitors for sulfation in the GI wall my increase ethinyl estradiol bioavailability (e.g., ascorbic acid)."

- **Hepatic metabolism:** "Interactions can occur with drugs that induce microsomal enzymes which can decrease ethinyl estradiol concentrations (e.g., rifampin, barbituates, phenylbutazone, phenytoin. griseofulvin)."

- **Interference with Enterohepatic Circulation**: "Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce ethinyl estradiol concentrations (e.g., ampicillin, and tetracycline)."

- **Interference in the Metabolism of Other Drugs:** "Ethinyl estradiol may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased or decreased, respectively (e.g., cyclosporin, theophylline)."

THE REMAINDER OF THE LABELING TEXT REMAINS THE SAME

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

Please delete the last two sentences in the first paragraph of the Clinical Pharmacology Section as follows (shown by strike-out):

Clinical Pharmacology

> "Combination oral contraceptives primarily act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucous (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). ~~Gonadatropin suppression leads to decreased ovarian production of androgens including testosterone. Additionally, Triphasil increases sex hormone binding globulin (SHBG), resulting in lowere serum free testtosterone."~~

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted March 19, 1998). These revisions are terms of the NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-190/S-034, 19-192/S-033." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M. D., M.P.H.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research